31

THE C-TERMINAL TAIL OF TACHYKININ RECEPTORS IS A REGULATORY DOMAIN INFLUENCING GROWTH CONTROL AND MALIGNANT POTENTIAL. C.A. Haskell, M. Sharif, N. Sasakawa, M.R. Hanley. Department of Biological Chemistry, School of Medicine, University of California at Davis, Davis, CA 95616-8635.
The neuroactive tachykinin peptides, Substance P, Substance K and Neuromedin K, signal through activation of the G-protein coupled receptors NK1, NK2 and NK3 respectively. These receptors share a common signaling mechanism in activation of phospholipase C. Nevertheless, these structurally similar receptor subtypes differ dramatically in their abilities to induce proliferation and malignant transformation when ectopically expressed. Specifically, we have examined cloned rat tachykinin receptors expressed in NIH3T3 fibroblasts. In these cells, the NK1 receptor is mitogenic, but not oncogenic; the NK3 is neither mitogenic nor oncogenic; and the NK2 receptor is oncogenic. The possible role of the divergent C-terminal tail region in programming these distinctive growth responses was evaluated using progressive premature termination by PCR insertion of a stop condon. These mutant receptors were then expressed in NIH3T3 fibroblasts both in the presence and absence of the cognate ligand. Truncation converted the normal mitogenic activity of NK1 receptor to ligand-dependent malignant transformation; thus converting a candidate proto-oncogene to an active oncogene. The acquisition of malignant activity was correlated with a loss of normal agonist-dependent desensitization as assessed by expression in Xenopus oocytes. This approach has been extended to the NK2 and NK3 receptors. The results suggest that 1) alterations in desensitization may be one, but not the only component, in acquisition of new growth regulatory behavior in C-terminal tail mutation of these receptors, and 2) short sequences in the tail region are significant control elements in growth.

Neuropeptide Y

32

PHARMACOLOGICAL CHARACTERIZATION OF THE HUMAN Y2 RECEPTOR FROM THE KAN-TS NEUROBLASTOMA CELL LINE. E. Heuillet, T. Canton, Z. Bouaiche, J.C. Blanchard, A. Dobel. Rhone-Poulenc Rorer S.A., Neurochemistry Dept., CRVA8, Vitry/Seine, France.
Neuropeptide Y is thought to exert its CNS effects by interaction with three different receptors (Y1, Y2, Y3). This report describes the characterization of the human Y2 receptor. Using porcine [^{125}I]peptide YY as the radioligand, a single population of non-interacting high-affinity binding sites (Kd = 0.027 ± 0.003 nM; B_{max} = 348 ± 49 fmol/mg protein) was demonstrated. Human PYY competitively inhibited the specific binding of [^{125}I]peptide YY (IC_{50} = 0.11 ± 0.02 nM) and decreased the forskolin-stimulated cAMP production (EC_{50} = 0.15 ± 0.05 nM) with a maximal inhibition of 59 ± 4% at 10^{-8} M. The rank order of potency of NPY and related peptides at these human Y2 receptors (PYY≥NPY>NPY(13-36)>>[Leu^{31},Pro^{34}]NPY) is similar to that at Y2 receptors in rat hippocampus and different from that at human Y1 receptors. The chimeric peptide M32, (galanin(1-13)-NPY(25-36)), which is a very potent agonist at the human galanin receptor is also a potent Y2 agonist. The inhibition of the cAMP formation was abolished by pertussis toxin, suggesting the activation of a G-protein dependent process. The KAN-TS cell line thus appears to be a relevant tool for the study of human Y2 receptor.

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